**Acute promyelocytic leukemia**
- Associated with disseminated intravascular coagulation (DIC)
- Bilobed blasts with granules +/- Auer rods
- Sensitive to ATRA/arsenic trioxide
- **PML/RARA; t(15;17)(q24.1;q21.2)**
- Other variants:
  - **NUMA1/RARA; t(11;17)(q13.4;q21.2)**
  - **NPM1/RARA; t(5;17)(q35.1;q21.2)**
  - **STATSB/RARA; t(17;17)(q21.2;q21.2)**
  - **ZBTB16/RARA (formerly PLZF/RARA); t(11;17)(q23.2;q21.2)**
- Cells with regular nuclei, many granules, absence of Auer rods, pelgeroid neutrophils, strong MPO
- **ZBTB16/RARA and STATSB/RARA are ATRA resistant**

**Core Binding Factor (CBF) AML**
- **RUNX1/RUNX1T1; t(8;21)(q22;q21.2)**
- Blasts with basophilic cytoplasm, azurophilic granules and perinuclear hofs; may show pseudo-Chédiak-Higashi granules
- Neutrophils may show pseudo-Pelger-Huët nuclei and salmon pink granules
- Often single, long Auer rods with tapered ends
- Presence of KIT mutation and CD56 expression associated with worse prognosis
- **ASXL1/2 mutations may also be seen**
- **CBFB/MYH11; inv(16)(p13.1q22) or t(16;16)(p13.1;q22)**
- Blasts with abnormal eosinophils (showing immature eosinophilic/basophilic granules, dense and purple-violet in color)
- May be a subtle rearrangement only seen with FISH or RT-PCR
- Secondary cytogenetic abnormalities include +22 and +8 (each occurring in 10-15% of cases), del(7q) and +21 (in 5% of cases)
- **KIT mutations in exons 8 and 17 found in 30-40% of cases; worse prognosis**
- **Other mutations: NRAS (45% of cases), KRAS (13% of cases), FLT3 (14% of cases)**

**Acute Myeloid Leukemia with Recurrent Genetic Abnormalities**

<table>
<thead>
<tr>
<th>Good prognosis</th>
<th>Intermediate prognosis</th>
<th>Poor prognosis</th>
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<tbody>
<tr>
<td>AML with t(9;11)(p21.3;q23.3); KMT2A/MLLT3</td>
<td>Often monoblasts and promonocytes</td>
<td>AML with t(6;9)(p23;q34.1); DEK/NUP214</td>
</tr>
<tr>
<td>- Often present with DIC, myeloid sarcoma, gingival hyperplasia</td>
<td>May present with DIC, myeloid sarcoma, gingival hyperplasia</td>
<td>- Blasts with/without monocytic features</td>
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<tr>
<td>- &gt;120 different translocations involving KMT2A</td>
<td>Translocations involving MLLT1, MLLT10, AFDN or ELL often result in AML, although translocations involving KMT2A may also result in lymphoblastic leukemia</td>
<td>- Associated with basophilia and multilineage dysplasia</td>
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<tr>
<td>- Translocations may be subtle, requiring FISH/other molecular techniques for identification</td>
<td>Translocations may involve MECOM overexpression is common; worse prognosis</td>
<td>- FLT3-ITD mutations are common; may benefit from FLT3 inhibitors</td>
</tr>
<tr>
<td>- MECOM overexpression is common; worse prognosis</td>
<td>AML with inv(3)(q21.3;q26.2)</td>
<td>AML with inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM</td>
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<tr>
<td>- Often associated with increased dysplastic megakaryocytes with monolobated or bilobed nuclei, and multilineage dysplasia</td>
<td>- May have normal or elevated platelet counts, hepatosplenomegaly</td>
<td>- Associated with increased dysplastic megakaryocytes with monolobated or bilobed nuclei, and multilineage dysplasia</td>
</tr>
<tr>
<td>- Often associated with monosomy 7 (&gt;50% of cases), del(5q) and complex karyotypes</td>
<td>Peripheral blood may include hypogranular neutrophils with pseudo-Pelger-Huët nuclei, giant and hypogranular platelets with bare megakaryocyte nuclei</td>
<td>- Often associated with monosomy 7 (&gt;50% of cases), del(5q) and complex karyotypes</td>
</tr>
<tr>
<td>- Also associated with mutations of RAS/receptor tyrosine kinase signalling pathways (NRAS, PTPN11, FLT3, KRAS, NF1, KIT)</td>
<td>Associated with increased dysplastic megakaryocytes with monolobated or bilobed nuclei, and multilineage dysplasia</td>
<td>- Other associated mutations: GATA2, RUNX1, SF3B1</td>
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<td>- Other associated mutations: GATA2, RUNX1, SF3B1</td>
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*“Molecular in My Pocket” reference cards are educational resources created by the Association of Molecular Pathology (AMP) for laboratory and other health care professionals. The content does not constitute medical or legal advice, and is not intended for use in the diagnosis or treatment of individual conditions. See [www.amp.org](http://www.amp.org) for the full “Limitations of Liability” statement.*
### AML with recurrent genetic abnormalities (cont’d)

<table>
<thead>
<tr>
<th>AML with BCR/ABL</th>
<th>AML with mutated NPM1</th>
<th>Acute myeloid leukemia with gene mutations</th>
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<tbody>
<tr>
<td>- Provisional entity&lt;br&gt;- De novo AML in patients with no evidence of CML before/after therapy&lt;br&gt;- Present with less splenomegaly, less basophilia, lower cellularity, fewer dwarf megakaryocytes, normal M:E ratio compared with blast transformation of CML&lt;br&gt;- Most cases show the p210 fusion (most commonly b2a2 and b3a2 fusions); minority show p190 fusion&lt;br&gt;- Associated with -7, +8 and complex karyotypes&lt;br&gt;- May be associated with NPM1 and FLT3-ITD, loss of IKZF1 and CDKN2A and cryptic deletions in IGH and TRG genes (not seen in blast transformation of CML)</td>
<td>- Blasts often show monocytic features&lt;br&gt;- Multilineage dysplasia seen in up to 25% of cases&lt;br&gt;- Often associated with normal karyotype&lt;br&gt;- del(9q), +8 seen in 5-15% of cases&lt;br&gt;- Secondary mutations include FLT3, DNMT3A, IDH1/2, KRAS, NRAS&lt;br&gt;- Overall good prognosis; poorer prognosis with presence of FLT3-ITD +/- DNMT3A</td>
<td>- &gt;70% of cases associated with normal karyotype; del(9q) may also be seen&lt;br&gt;- GATA2 mutations seen in 39% of cases, FLT3-ITD in 5-9% of cases&lt;br&gt;- Biallelic mutation associated with good prognosis</td>
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### AML with myelodysplasia-related changes

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<th>Diagnosis requires:</th>
<th>Therapy-related myeloid neoplasms</th>
<th>Other</th>
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<tr>
<td>- &gt;20% blasts (blood/bone marrow)&lt;br&gt;- Either: History of MDS or MDS/MPN OR MDS-related cytogenetic abnormality OR multilineage dysplasia (&gt;50% dysplasia in ≥2 lineages)&lt;br&gt;- Absence of prior cytotoxic or radiation therapy for unrelated disease OR AML-defining recurrent cytogenetic abnormality&lt;br&gt;- May be associated with mutations of U2AF1, ASXL1, TPS3 (latter two mutations worsen prognosis)</td>
<td>- Occurs as a complication of cytotoxic (e.g. alkylating agents, topoisomerase II inhibitors) and/or radiotherapy for neoplastic/non-neoplastic disorders&lt;br&gt;- May also be associated with antimitabolites (thiopurines, mycophenolate mofetil, fludarabine) and antitubulin agents (vincristine, vinblastine, vindesine, paclitaxel, docetaxel), hydroxyurea, L-asparaginel, and purine analogues)&lt;br&gt;- Associated with abnormal karyotype, most often del(5q), -7, del(7q) in &gt;70% of cases&lt;br&gt;- &gt;80% of cases with del(5q) have TP53 mutations or losses with del(17p) or -17&lt;br&gt;- 20-30% of cases have balanced translocations including t(15;17) and inv(16)&lt;br&gt;- Mutated genes of unknown significance include TET2, PTPN11, IDH1/2, NRAS, and FLT3&lt;br&gt;- Poor prognosis</td>
<td>- PDGFRB rearrangement (often del(4)(q12q12); FIP1L1/PDGFRB)</td>
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### AML with mutated RUNX1

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<thead>
<tr>
<th>AML with mutated RUNX1</th>
<th>Myeloid Neoplasms with Germline Predisposition</th>
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<tr>
<td>- May be AML with minimal differentiation, AML with maturation or show monocytic features&lt;br&gt;- Mutations may occur with +8 and +13&lt;br&gt;- Other associated mutations: ASXL1, KMT2A partial tandem duplication, FLT3-ITD, IDH1 R132, IDH2 R140 and R172, SRSF2, EZH2 and STAG2&lt;br&gt;- Subset of these patients have germline RUNX1 mutations; assess family history&lt;br&gt;- Show poor prognosis</td>
<td>- AML with germline CEBPA mutation&lt;br&gt;- Myeloid neoplasm with germline DDX41 mutation&lt;br&gt;- Associated with platelet disorders&lt;br&gt;- RUNX1, ANKRD26, ETV6 mutations&lt;br&gt;- Associated with other organ dysfunction&lt;br&gt;- GATA2 mutation&lt;br&gt;- JMML type mutations</td>
</tr>
</tbody>
</table>

#### MDS-defining cytogenetic abnormalities

- Complex karyotype (>3 abnormalities)
- Unbalanced abnormalities
  - -7 or del(7q)
  - del(5q) or t(5q)
  - Isochromosome 17q or t(17q)
  - -13 or del(13q)
  - del(11q)
  - del(12p) or t(12p)
  - idic(X)(q13)
- Balanced abnormalities
  - t(11;16)(q23;p13.3)
  - t(3;21)(q26.2;q22.1)
  - t(1;3)(p36.3;q21.2)
  - t(2;11)(p21;q23.3)
  - t(5;12)(q32;p13.2)
  - t(5;7)(q32;q11.2)
  - t(5;17)(q32;p13.2)
  - t(5;10)(q32;q21)
  - t(3;5)(q25.3;q35.1)